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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,393	07/10/2001	Keith D. Allen	R-387	9468

26619 7590 09/09/2004

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EXAMINER	
SHUKLA, RAM R	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,393	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's response file 6/10/04 is acknowledged.
2. Claims 1-29 have been cancelled.
3. New claims 30-35 have been entered.

Specification

4. The objection to incorporation of subject matter into this application by reference to US non-provisional and provisional applications on pages 10 and 11 is maintained for reasons of record set forth in the previous office action of 12/5/03.

Response to Arguments

Applicant's arguments filed 6/10/04 have been fully considered but they are not persuasive. Applicants argue:

> However, Applicant submits that the material incorporated by reference in the instant application is not essential material, *i.e.* is not required in order to make the specification enabling. More particularly, the descriptions of the subject matter of the applications, which follow each attempt to incorporate the applications by reference (see page 10-11), are sufficient to enable the skilled artisan to practice the invention as claimed. As such, the Examiner's objection is improper, and Applicant requests that it be withdrawn.

However, these arguments are not persuasive since the material incorporated is essential material. For example, page 10, lines 29-31 describes preparation of a targeting construct used in a preferred embodiment of the present invention. Likewise, page 11, lines 11-16 describe yet another construct that is essential for another embodiment. Both these incorporations (of subject matter from US applications) are therefore essential.

5. Applicants' correction of the drawings and sequences is acknowledged.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 30-35 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility for reasons of record set forth in the previous office action of 12/5/03.

Response to Arguments

Applicant's arguments filed 6/10/04 have been fully considered but they are not persuasive. Applicants argue:

> Applicant submits that the transgenic mouse and related methods and compositions as claimed are supported by a specific and substantial utility or well-established utility. More particularly, the specification demonstrates disruption of a gene comprising the sequence set forth in SEQ ID NO:1 in a mouse, which results in a specific phenotype of increased pain sensitivity and/or increased susceptibility to seizure. The transgenic mouse would clearly be useful for identifying agents capable of modulating the claimed phenotypes. The desire in the art for discovering treatments and methods of modulating pain and/or seizure establishes the claimed transgenic mice as having a well-established utility. The skilled artisan would recognize the utility and value of such an *in vivo* model for these conditions or disorders.

However, recitation of SEQ ID NO 1 does not alter the utility issues discussed in the previous office action because the function of the protein encoded by SEQ ID NO 1 has not been established either in the specification or in the art of record. Additionally, claim 30 as instantly presented recites a transgenic mouse whose genome comprises a disruption in a gene comprising SEQ ID NO 1, which is a cDNA and there is no mouse genome of record that would comprise a cDNA sequence therefore, how can there be a utility for a transgenic mouse that could not possibly exist. Additionally, as discussed in the enablement rejection in the previous office action and further discussed below, there is no evidence that limulus clotting factor has any association with pain or seizure and that pain and seizure are non-specific phenotypes that vary even among species of mouse. Therefore, the claimed

transgenic mouse could not be used for identifying agents that modulate limulus clotting factor gene function since the phenotype of the mouse is not related to limulus clotting factor function.

8. Claims 30-35 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/ or substantial asserted or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention for reasons of record set forth in the previous office action of 12-5-03 and as discussed above.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 30-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record set forth in the previous office action of 12/5/03.

In view of new claims being drawn to a transgenic mouse and method of producing and method of using the mouse, the enablement issues related to general nature of transgenesis and method of making and using any transgenic non-human animal is moot. However, the issues relating to the enablement of a transgenic mouse as reiterated below remain and are maintained.

The specification on pages 52-54 teaches generation of a homozygous transgenic mouse using a targeting construct described in figure 2 and the transgenic mouse shows decrease in response to latency to hot plate and a decreased response threshold to metrazol, however, there is no evidence as to what is the relationship of the phenotype of the claimed mouse to the protein which was disrupted. While the transgenic mouse displayed changes in pain perception, the presence of these phenotypes in a transgenic mouse may not be predictable of the gene disruption, rather it may be due to genetic background. Lariviere et al (Lariviere et al The Journal of Pharmacology and Experimental Therapeutics 297:467-473, 2001) noted:

"We show that the 129 and C57BL/6 mouse strains, which provide the default genetic background on which null mutants are constructed, display significant and sometimes extreme phenotypic differences in may assays of nociception, hypersensitivity, and analgesia."

It is noted that the mice used in the generation of the instantly claimed mouse were also 129/OlaHsd and C57BL/6. Therefore, the phenotype observed in the mice of the instant invention may be due to genetic variation as discussed by Lariviere et al, and not due to the gene disruption.

Furthermore, Lariviere et al noted that the most common criticism is that compensatory effects of other genes may either mask the detection of the targeted gene's phenotype or alternatively be confused for the phenotype of the null gene (see first paragraph in the left column on page 467). In view of the lack of any information about the function of the disrupted gene in the instant application, it will be unpredictable whether the phenotype observed is due to the gene recited or any other gene.

It is emphasized that the instantly presented claims recite a transgenic mouse whose genome comprises a disruption in a gene comprising SEQ ID NO 1, which is a cDNA and there is no mouse genome of record that would comprise a cDNA sequence therefore, how can an artisan use a transgenic mouse that could not possibly exist. Furthermore, it is not even established whether the sequence disclosed in SEQ ID NO 1 encodes a full length protein which has any function. It is

noted that SEQ ID NO 1 is an EST sequence disclosed in Genbank accession no. AA830210 which is a 369 nt long cDNA isolated from a cDNA library prepared from germinal center B cells and there is no evidence that this cDNA encodes a protein or any protein with any function and neither the specification nor the applicants have provided any evidence for this.

Therefore, an artisan of skill would not know how to use the claimed transgenic mouse in view of the unpredictability of the phenotype and unpredictability of the relationship of the phenotype to the gene disrupted. In other words, an artisan of skill would not have been able to practice the claimed methods of identifying agents using the transgenic mouse or transgenic animal.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictablility of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use any and all embryonic stem cells. It is noted that the unpredictability of a particular area may alone provide reasonbale doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).

Response to Arguments

Applicant's arguments filed 6/10/04 have been fully considered but they are not persuasive. Applicants argue:

> less likely due to the 129 strain background, or a hitchhiking donor gene. Lariviere *et al.* fail to provide any evidence or examples suggesting that the increased pain sensitivity phenotype, as observed by Applicant in the claimed mice, is a result of anything other than disruption of the target gene.

It is noted that Lariviere et al has provided evidence that pain sensitivity phenotype is no a reliable phenotype and is a non-specific phenotype which varies even among species of mouse. Therefore, applicants have to provide evidence that the pain or seizure phenotype in the claimed transgenic mouse is a specific

phenotype associated with the gene disrupted and the applicants have failed to provide any evidence in this regard.

11. The written description rejection is moot in view of the cancellation of claims and the new claims being drawn to a transgenic mouse with a phenotype.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 30-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 30-35 are indefinite because they recite a transgenic mouse whose genome comprises a gene comprising SEQ ID NO 1 which is a cDNA. It is unclear as to how a genome can comprise a cDNA.

Claim 35 is indefinite because it recites the term "a condition associated with a disruption in a....", the metes and bounds of which are unclear.

14. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (571) 272-0735 . The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The fax phone number for TC 1600 is (703) 872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (571) 272-0532.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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